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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,251	12/07/2004	Phillip Mark Hogarth	4602AL-1	2961

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,251	HOGARTH ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction requirement was received on 3/10/2006. Claims 1-12 are pending in the instant application. Applicant's election without traverse of Group I, claims 1-12, drawn to a method for screening a compound that is able to suppress aberrant immune activity in a non-human animal modified to express the human FcγRIIA receptor, is acknowledged. Applicant cancelled claims 6 and 13-42 and amended claims 1-3.

Claims 1-5 and 7-12 are currently under consideration.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Drawing 4, lists section 4(A); which is not disclosed in the brief description of the drawings (Specification, pg. 7). Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either

"Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims encompass a method of screening a non-human transgenic animal, or cell derived from said animal, for a compound that is able to suppress aberrant immune activity, such as an autoimmune disease. Wherein said non-human transgenic animal is any species of animal and has been genetically modified by any means to express the human FcγRIIA receptor, so that said animal is resistant to collagen-induced arthritis prior to being modified to express the human FcγRIIA receptor.

The claims read on a method for screening a compound using a non-human animal made by genetic modification to a non-human animal after it is born, so that said animal is resistant to collagen-induced arthritis prior to being modified to express the human FcγRIIA receptor. It is noted that the term transgenic is used in the art to denote animals that are capable of germline

transmission of said transgene. Such transgenic animals are generally made through techniques such as pro-nuclear injection or injection of modified ES cells into blastomeres. However, the claims are drawn to a non-human transgenic animal that is resistant to collagen induced arthritis prior to being modified to express the human FcγRIIA receptor. This language indicates that the non-human transgenic animal is at least a neonate and is genetically modified after birth. This raises issues of post partum gene transfer. However, the specification does not provide any guidance on any methods of making such genetic modifications to a post partum non-human animal, or that said modifications could be made in a fashion that modify the germline and can be passed on to subsequent generations, a trait that is required by the claimed transgenic non-human animal. The only non-human transgenic animal genetically modified to express the human FcγRIIA receptor, disclosed in the specification, is the human FcγRIIA receptor transgenic mouse made by Mckenzie et al. (Specification, pg. 12, lines 30-32). Mckenzie et al. describes three different mouse strains that were genetically modified to express the human FcγRIIA receptor. (pg. 4316, Figure 6). The mice were all constructed using standard embryonic transgenic techniques and are capable of germline transmission of the human FcγRIIA receptor transgene {McKenzie et al. (1999) J. Immunol. 162: 4311-4318; Abstract, Pg. 4312, Materials and Methods}. McKenzie et al. does not provide any guidance on genetically modifying a post partum non-human animal so that it expresses the human FcγRIIA receptor, is resistant to collagen induced arthritis prior to being modified to express the human FcγRIIA receptor, and is capable of germline transmission of the gene encoding the human FcγRIIA receptor. Further, at the time of filing, it was unknown in the art on how to make a transgenic animal by gene transfer into a post-partum animal, so that the gene was transmitted to subsequent generations. See Wall

et al. (2002) Theriogenology 57:189-201; Abstract. This was due to issues of integration of the transferred gene into the germ cells with a lack of sufficient efficiency to insure transmission to subsequent generations. Finally, neither the specification, nor the art of record at the time of filing, provide any guidance on how to make a non-human animal less resistant to collagen-induced arthritis by modifying said animal to express the human FcγRIIA receptor. The specification does not provide any guidance on the type of construct, promoter, target tissues, or mode of administration for post-partum gene transfer in order to induce the claimed phenotype in any non-human animal. Due to the lack of guidance in the specification on how to make transgenic non-human animals via post partum gene transfer, and the teachings in the art, it would have required undue and extensive experimentation for the skilled practitioner to figure out for himself how to make a transgenic animal using such a method.

Genetic modification to an adult animal in the context of post partum gene transfer raises identical issues related to unpredictability as those confronted in gene therapy. Verma et al. states that in the past, the Achilles heel of gene therapy was gene delivery, and that, most approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. These issues remain as current problems in the field of gene therapy. Pfeifer and Verma state that even "though gene therapy holds great promise for the achievement of this task, the transfer of genetic material into higher organisms still remains an enormous technical challenge {Pfeifer and Verma (2001) Annu. Rev. Genomics. Hum. Genet. 2:177-211; pg. 177, pgph 1}. Johnson-Saliba et al. concurs stating, "although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches,

especially when non-viral vectors are used, is the poor efficiency of DNA delivery." {Johnson-Saliba et al. (2001) Curr. Drug. Targets 2:371-99; Abstract}. Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based-medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non-toxicity, non-pathogenicity, non-immunogenicity, [and] non-tumorgenicity." {Shoji et al. (2004) Current Pharmaceutical Design 10 :785-796}. The long-standing problems related to gene transfer and expression are not solved by the disclosure of the instant application. The specification does not provide any guidance on the vector/promoter combination to be used, the amount of vector to be administered, or the level of human FcγRIIA receptor expression required to produce decreased resistance to collagen-induced arthritis in the genetically modified non-human animal. Further, when the problems of inducing a specific phenotype via post-partum gene transfer are combined with those of germline transmission, as reviewed above, the skilled practitioner would be reduced to guessing as to how to make a non-human animal via this methodology for use in the claimed method. Such guessing would require undue and extensive experimentation.

It is again noted that applicant claims the human FcγRIIA receptor non-human animal in such a manner so as to read specifically on non-human animals modified by post-partum gene transfer. However, even if the claims are broadly construed to encompass human FcγRIIA receptor transgenic non-human animals made by traditional techniques, the specification does not provide sufficient guidance to make any non-human animal commensurate in scope with the claim. This is due to the unpredictability of making any non-human transgenic animal, with a

specific phenotype. The only human FcγRIIA receptor transgenic non-human animal disclosed in the instant application is the human FcγRIIA receptor transgenic mouse made by Mckenzie et al. (Specification, pg. 12, lines 30-32; pg. 18, lines 15-20). It is noted that all of the working examples involving the claimed method were practiced using the mouse of Mckenzie et al. (Specification Examples 1-10). However, the guidance provided by Mckenzie et al. does not provide sufficient guidance to enable the manufacture of any human FcγRIIA receptor non-human animal, that shows reduced resistance to collagen-induced arthritis.

The manufacture of transgenic animals with a given phenotype are sensitive to factors such as the integration site of the transgene, copy number as well as the genetic background of the animal used. This observation is supported by Houdebine et al., who states that "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" {Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2:The expression of transgenes}. Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic animals and the level of expression of transgenes in mice is not predictive of their levels in other animals (pg. 310, col. 1, pgph 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col.1, pgph 3). See also Kolb et al., who states that "the expression of foreign genes in transgenic animals is generally unpredictable as transgenes integrated at random after pro-nuclear injection into fertilized oocytes" because of inhibition by neighboring chromatin {Kolb et al. (1999) Gene 227:21-31; Abstract}. Sigmund, C., concurs, reporting that variation in the genetic background contributes

to the unpredictability of the resulting phenotypes of transgenic or gene-targeted animals {Sigmund, C., (2000) Arterioscler. Thromb. Vasc. Biol., p. 1425-1429}. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Even within a single species such as mice, the variation in phenotype penetrance can be seen different strains of mice transgenic for the human FcγRIIA receptor (McKenzie et al., pg. 4316, Fig. 6). The human FcγRIIA receptor transgenic mouse line 32 had a 6 fold less severe induction of thrombocytopenia in response to antibody exposure than did mouse line 11 (McKenzie et al., pg. 4316, Fig. 6). This indicates that that the phenotype of said mice is due to epigenetic interactions and not just the presence of the human FcγRIIA receptor transgene. Thus, based on the art recognized unpredictability of making any transgenic non-human animal with a specific phenotype, in species other than mice, and in view of the lack of guidance provided by the specification for making any transgenic non-animal with the claimed phenotype, the skilled artisan would not have had a reasonable expectation of success in generating the claimed genus of transgenic non-human animals without engaging in undue and extensive experimentation.

Finally, as stated previously, the only non-human transgenic animal genetically modified to express the human FcγRIIA receptor, disclosed in the specification, is the human FcγRIIA receptor transgenic mouse made by Mckenzie et al. (Specification, pg. 12, lines 30-32). Mckenzie et al. describes three different mouse strains that were genetically modified to express the human FcγRIIA receptor. (pg. 4316, Figure 6). Mckenzie et al. describes the characterization of two mouse strains that were transgenic for the human FcγRIIA receptor, on a wildtype

background (pg. 4316, Figure 6). These two mice lines had clear differences between each other in their platelet counts following antibody induced thrombocytopenia (pg. 4316, Figure 6). Further, Mckenzie et al. describes the characterization of a mouse strain that was transgenic for human FcγRIIA receptor, on an endogenous Fcγ knockout background (pg. 4316, Figure 6). The specification does not indicate which of these three different mouse strains, characterized by Mckenzie et al., were used in the exemplary methods. Further, neither McKenzie et al., nor the specification, teaches which of the three mouse lines taught by McKenzie et al., is resistant to collagen-induced arthritis prior to being genetically modified to express human FcγRIIA receptor. Therefore the skilled practitioner would be unable to determine if the method can be practiced with any non-human animal genetically modified to express the human FcγRIIA receptor on a wild type background, since the results of Mckenzie et al. indicate that there are issues with penetrance in regards to phenotype, even with mice lines carrying the identical transgene. Further, given that applicant does not specify whether or not the mouse used in the claimed method is an endogenous Fcγ knockout, the skilled practitioner would have to determine for himself whether the presence of endogenous Fcγ receptors interfered with the practice of the claimed method for any non-human transgenic animal genetically modified to express the human FcγRIIA receptor. Since applicant does not provide guidance in the specification as to what level or expression pattern of human FcγRIIA receptor are required in order to practice the claimed method, or whether endogenous Fcγ receptors interfere with the claimed method, the skilled practitioner would be forced to make multiple non-human animals expressing the human FcγRIIA receptor in order to asses their phenotype and the applicability of any resulting strain in the claimed method. Because McKenzie et al. reports variation in the phenotypes of different

mouse lines transgenic for the human FcγRIIA receptor transgene this strongly indicates that the mouse line disclosed in the specification has a unique phenotype that is specific for the genotype (including both transgene and the genetic background of the disclosed mouse) of the specific mouse line used. Sigmund provides guidance that some specific phenotype/genotype associations in mouse strains are unique. Sigmund states that in regards to mice "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype." (pg, 1425, col. 1, Introduction) These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction). Sigmund concludes by stating that "in the absence of inbred strains, there is no optimal set of experimental and control conditions that normalizes the epigenetic effects of unlinked loci," and that each transgenic mouse strain must be assessed as to whether the phenotype observed is due specifically to the targeted modification or is affected by other loci (pg. 1428, col. 1, Guidelines). Therefore in view of the general issues of unpredictability recognized in the art of mouse transgenics and the specific teachings of McKenzie et al., about the variations in penetrance between different mouse lines transgenic for the human FcγRIIA, the skilled practitioner would be required to engage in undue and extensive experimentation in order to reliably predict out how the claims could be practiced with any mouse strain genetically modified to express the human FcγRIIA receptor.

Therefore, given the lack of guidance in the specification on post partum gene transfer, the lack of guidance on the specific mouse used in the working examples, the teachings in the art

on the unpredictability on gene transfer in adult animals, and the teachings in the art on the unpredictability of making non-human transgenic animals, the skilled practitioner would be unable how to practice the claimed method without undue and extensive experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It is noted that applicant's claims are not considered enabled as presently drafted. This is due in part to the lack of description in the specification on the genetic background of the mice used in the exemplary methods. However, the claims have been broadly construed to include human FcγRIIA receptor transgenic mice made by standard transgenic techniques that have a decreased resistance to collagen induced arthritis in comparison to un-genetically modified mice.

Claims 1,2,7-9 rejected under 35 U.S.C. 102(b) as being anticipated by McKenzie et al. {McKenzie et al. (1999) J. Immunol. 162: 4311-4318}.

McKenzie et al. provides guidance on a human FcγRIIA receptor transgenic non-human mouse on a C7BL/6 XSJL background (Abstract; pg. 4312, Materials and Methods). Mckenzie et al. describes three different mouse strains that were genetically modified to express the human FcγRIIA receptor (pg. 4316, Figure 6). Mckenzie et al. describes the characterization of two mouse strains that were transgenic for human FcγRIIA receptor, on a wild type background (pg. 4316, Figure 6). Further, Mckenzie et al. describes the characterization of a mouse strain that

was transgenic for human FcγRIIA receptor, on an endogenous Fcγ knockout background (pg. 4316, Figure 6). It is noted that the exemplar human FcγRIIA receptor transgenic non-human animal disclosed in the instant application is one of the human FcγRIIA receptor transgenic mouse made by Mckenzie et al. (Specification, pg. 12, lines 30-32; pg. 18, lines 15-20). This mouse inherently has decreased resistance to collagen-induced arthritis in comparison to control animals (Specification, pg. 27, Example 7). McKenzie et al. teaches that the mice can be used as a model of autoimmune thrombocytopenia (pg. 4313, co. 2; pg. 4316, col. 1, Figures 5 and 6). Wherein thrombocytopenia is assessed in terms of platelet counts. (pg. 4316, Figures 5 and 6). Mckenzie et al. teaches that the FcγRIIA receptor transgenic non-human mouse provides a mechanism for screening therapeutic modalities (pg. 4317, col. 2). Finally, Mckenzie et al. states that the therapeutic treatments to be tested should be directed at the expression or function of the FcγRIIA receptor. Thus, by teaching all the limitations of the claims as written, Mckenzie et al. anticipates the instant invention as claimed.

No Claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that

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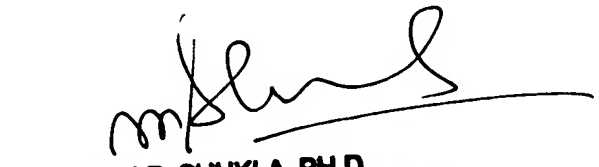

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